Please add new claims 26-28.

-- 26. A method of using the polymersome vesicle of claim 3, wherein the method comprises:

preparing the polymersome vesicle;

encapsulating therein at least one encapsulatable material; and

using the polymersome, which comprises at least one encapsulated material, for exporting said encapsulated material(s) contained therein into the environment immediately surrounding the polymersome.

27. The method of claim 26, wherein the environment is in a patient, and wherein the method further comprises exporting the encapsulatable material from the patient into the polymersome, thereby permitting its removal from the patient.

28. The method of claim 27, wherein the method further comprises removing the polymersome and the material encapsulated therein from the patient, wherein the encapsulated material is selected from the group consisting of a drug, therapeutic composition, medicament, dye, indicator, nutrient, sugar, vitamin, mineral, protein or protein fragment, salt, electrolyte, gene or gene fragment, product of genetic engineering, steroid, adjuvant, biosealant and gas. --

Remarks

Although the claims have been amended by Preliminary Amendment to more clearly define the method of using the polymersomes of claims 15, 16 and 23 and new claims 26-28 have been added, no new matter has been added to the application. The amendment is fully supported by the specification and by claims 15-24 as previously written.

Response to the rejections under 35 USC §112, second paragraph and 35 USC §101

The Examiner has rejected claims15-16 and 21-24 under 35 USC §112, second paragraph. Applicants appreciate the comments made by the Examiner regarding the requirements under 35 USC §112, second paragraph, in light of which Applicants have cancelled claims 21, 22 and 24, amended claims 15-16, and added new claims 26-28. In light of the amendments, which clearly describe the method steps in the subject pending claims, the

Examiner's rejection under 35 USC §112, second paragraph is now moot, and Applicants respectfully request that the entire rejection be withdrawn.

Similarly, the Examiner has made a new rejection of claims15-16 and 21-24 under 35 USC §101 on the premise that the cited claims, failing to set forth steps, also fail to properly define a process. Applicants respectfully point out that the cited claims have been amended to physically show the steps as separately indented lines under the preamble. The claims previously did include steps relating to the method of use of Applicants' invention, but the steps were not separately indicated. Nevertheless, in light of the amendments, which clearly describe method steps in the subject pending claims, the Examiner's rejection under 35 USC §101 is now moot. Accordingly, Applicants respectfully request withdrawal of the rejection, and that the claims be held allowable.

Response to the rejections under 35 USC §102(b) regarding Henzelwood, Hajduk, Ding, Fendler, or Cornelissen

The Examiner has rejected claims 1-4, 10, 13-15 and 25 under 35 USC § 102(b) as anticipated, over Henzelwood (*Macromolecules,* 1998) or Hajduk (*J. Phys. Chem.*, 1998) or Ding (*J. Phys. Chem.*, 1998) or Cornelissen (*Science*, 1998) or Fendler (*Science*, 1998) for essentially the reasoning previously of record. In making this rejection, the Examiner states that each of the cited references teaches polymeric vesicles having a membrane, wherein according to the abstracts of each, the polymers are diblock polymers. In view of this work, the Examiner has rejected Applicants' invention.

However, contrary to the Examiner's interpretation of the prior art, the issue turns on the scientifically accepted definition of the term "vesicle," and on use of the term "vesicle," or lack thereof, in the cited references. Applicants' invention is defined as a polymersome vesicle comprising a semi-permeable, thin-walled encapsulating membrane, wherein the membrane is formed in an aqueous solution, and wherein the membrane comprises one or more synthetic super-amphiphilic molecules. In fact, none of the cited references teach polymeric vesicles, which must necessarily contain the following elements: (1) a thin-walled encapsulating membrane, (2) wherein the membrane is formed in an aqueous solution, and (3) wherein the membrane comprises one or more synthetic super-amphiphilic molecules. Consequently none anticipate Applicants' invention.

Regarding Henselwood and Hajduk

The Examiner offers a definition on page 4 line 15 of the outstanding Office Action: "micelles have a single membrane and are vesicles," and indicates that Henselwood's reference to "micelles" is, in fact, a recitation meaning "vesicles." However, according to the inventors, who are recognized scientists in the field, the Examiner's definition is incorrect. Nevertheless a Declaration is not necessary, because other evidence is presented below. Unfortunately, the Examiner offers no source for his definition, nor is a basis provided for the apparent conclusion that Henselwood, also recognized in his field, would not have known the difference between a "micelle" and a "vesicle," or that those authors actually meant a "vesicle," although they specifically describe the production of a "micelle."

"Vesicles," as the term is used in the present invention are defined at page 13, beginning at line 25. They are "essentially semi-permeable bags of aqueous solution as surrounded (without edges) by a self-assembled, stable membrane composed predominantly, by mass, of either amphiphiles or super-amphiphiles which self-assemble in water or aqueous solution." The membrane of a vesicle functions as a barrier to maintain a difference in composition and an osmotic balance between the interior of the vesicle and the exterior. At page 14, lines 19-21, an "encapsulating membrane" is defined as functioning to compartmentalize "by being semi- or selectively permeable to solutes, either contained inside or maintained outside of the spatial volume delimited by the membrane." Thus, a vesicle is a capsule formed in aqueous solution, which also contains aqueous solution. However, the interior or exterior of the capsule could also be another fluid, such as an oil or a gas. A "capsule," as the term is used in the present invention, is defined at page 14, lines 23-25, "the encapsulating membrane plus the space enclosed within the membrane."

Micelles are not equivalent to vesicles, nor are micelles a specific type of vesicle. As defined in Grant & Hackh's Chemical Dictionary, 5th Edition, 1987 a "vesicle" is a "small blister." Interestingly, Webster's Third New International® Dictionary (Unabridged, Copyright © 1993 by Merriam-Webster, Incorporated.) indicates that the Latin root "*vesicula*" denotes a "small bladder, small blister" and has the general form of a membranous cavity, which is defined as "a thin sac especially when filled with fluid." However, the same reference does not denote that a micelle is in any way related to a "sac" or a "bag," or even suggest a fluid filled membrane, as the term "vesicle" is used in the present invention. Rather Webster defines a

"micelle" as "a unit of structure built up from polymeric molecules or ions: as a highly associated particle of a colloidal solution." According to Grant & Hackh a "micelle" is "(1) an electrically charged, colloidal particle or ion, consisting of oriented molecules, (2) an oriented arrangement of a number of molecules, as in cellulose, (3) an aggregate of a number of molecules held loosely together by secondary bonds."

Thus, a vesicle is a far more specific object than a micelle. In fact, the suggestion that the molecules of a micelle are *loosely* held together would strongly suggest an inability to contain fluid. It certainly offers no indication of a membrane bound sac or bag from which release could be controlled. Accordingly, neither Henselwood (pg. 4, line 14) nor Hajduk (pg. 4, line 17) teach vesicles, nor do the authors mean "vesicles" when they refer to "micelles." The authors of the cited references make no mention of "vesicles" in the title, abstract, or results; nor is there any discussion or demonstration of such. This is because the authors of those references were well aware of the meaning of the term "micelle" when they elected to study the properties of micelles. They did not use the term "vesicle," because as individuals skilled in the art, they recognized the physical differences between a "micelle" and a "vesicle," and they knew that they were only examining and discussing micelles – not vesicles.

The disclosed structures in Henzelwood and in Hajduk are altogether lacking in any sort of membrane that separates an internal solution from an external solution. Hence, neither Henzelwood, nor Hajduk, anticipate the vesicles of the present invention. If the Examiner can provide *actual evidence* rather than opinion to the contrary, indicating that "micelles" and "vesicles" are actually one and the same, Applicants respectfully request that he do so before maintaining this rejection. This will permit Applicants to address the issue accordingly. Otherwise, Applicants submit that neither cited reference can anticipate the presently claimed invention.

Regarding Ding

Contrary to the Examiner's statement on pg. 4, line 19, with regard to Applicants' invention, which is defined as the preparation and use of *vesicles and related encapsulating membranes made in water from amphiphilic polymers and related molecules*, Ding does not teach aqueously-based "vesicular preparation on page 6108, col. 2, line 5 *et seq.*" Ding teaches vesicles prepared in organic solvents. More specifically, in the referenced page 6108, col.2, line 5 *et seq.*, Ding teaches vesicles only through addition of one organic solvent (*e.g.*,

tetrahydrofuran) into another organic solvent (*e.g.*, hexane). Ding does not teach vesicle formation in water or aqueous solution. Ding does not even teach vesicle formation in a single organic solvent. These are crucial distinctions from Applicants' invention. Not only is water less toxic, but water is critical for Applicants' applications, such as protein encapsulation, because proteins are known to denature in the presence of organic solvents. Thus, Ding cannot anticipate Applicants' claimed polymersome vesicle invention comprising a semi-permeable, thin-walled encapsulating membrane, wherein the membrane is formed in an aqueous solution, and wherein the membrane comprises one or more synthetic super-amphiphilic molecules.

Regarding Fendler

Contrary to the Examiner's assertion at page 4, line 20 that Fendler (1984) teaches "polymerized surfactant vesicles" according to its title, it does not teach Applicants' invention, which is defined as the "preparation and use of vesicles and related encapsulating membranes made in aqueous solution from amphiphilic polymers and related molecules" (see, *e.g.*, Field of Invention). In fact, regardless of the title, Fendler does not teach the preparation and use of vesicles and related encapsulating membranes made in water from amphiphilic polymers. Fendler teaches the formation of only structures from small lipid-like amphiphiles (lipid-like in molecular weight) with no more than four covalently cross-linkable bonds. The Fendler formulations, however, lack key characteristics of polymers, and only *after vesicle-type formation* does surfactant polymerization follow according to Fendler.

This is a crucial distinction from Applicants' invention because *post*-vesicle-formation polymerization would limit application of polymerized lipid vesicles. For example, as described by Fendler, such covalent polymerization is generally done with free radicals, which are widely known to readily damage encapsulants, such as proteins and DNA. As a result, Fendler fails to describe vesicles of the type disclosed in the present invention, which remain intact following either a cycle of dehydration and rehydration, or exposure to organic solvents (see, present application at page 3, lines 1-9). Applicants' invention, on the other hand, uses pre-polymerized polymers that assemble in water (and related aqueous solutions), without any need for additional covalent chemistry, or the addition of a solvent or reagents to drive polymerization. The 'Polymerized Surfactant Vesicles' described by Fendler are thus fundamentally different from Applicants' "polymer-surfactant vesicles" in that no additional chemistry is required once Applicants' vesicles are made.

Moreover, Applicants' polymersome membranes made from super-amphiphilic copolymers that incorporate an effective number of cross-linkable groups per co-polymer are cross-linked to form a contiguous, semi-permeable membrane. As proof of thorough cross-linking in the vesicles of the present invention, polymersomes with cross-linked membranes remain as intact vesicles, maintaining their encapsulated contents, after at least one cycle of dehydration and rehydration or exposure to organic solvents, such as chloroform (see, *e.g.*, FIG. 10, FIG. 11 or the specification at page 33, lines 10-14). Consequently, the amphiphiles taught by Fendler do not anticipate the cross-linked membrane of the polymersome vesicles of the presently claimed invention, nor can such amphiphiles anticipate the invention as a whole. See also inventors' recent manuscript attached to Applicants' response to the previous Office Action of record in this case.

Regarding Cornelissen

Finally, contrary to the Examiner's statement on page 5, line 1, that Cornelissen (1998) "teaches clearly the formation of vesicles by polymers (note the summary on page 1427)," the reference fails to teach Applicants' invention, which comprises "preparation and use of vesicles and related encapsulating membranes made in water from amphiphilic polymers" (see, *e.g.*, Field of Invention). Under but a single solution condition, Cornelissen reports (see legend of Fig. 2) the formation of "bilayer filaments," a "left-handed superhelix," and "collapsed vesicles." Thus, in light of the co-existence of multiple structures, Cornelissen teaches not vesicles alone, but multiple structures in co-existence. In other words, Cornellisen fails to provide a pure vesicle system.

Furthermore, the term 'collapsed,' as is known in the art, clearly indicates defects, which limit the ability of such "vesicles," if they can be so denoted, to encapsulate a liquid material. By comparison, Applicants' invention focuses on the use of wholly synthetic polymers (strictly synthetic super-amphiphiles) to form vesicles, rather than the naturally derivable di-alanine polymers (dipeptide polymers) used by Cornelissen. Moreover, Cornelissen makes no comparison to lipid or other vesicle-forming amphiphiles.

Importantly, Cornelissen also shows only vacuum-dried Transmission Electron Microscope (TEM) images of what are shown to be rods, helices, and loops. However, no images are provided by Cornellisen suggesting vesicles or vesicular systems. The authors fail to teach, suggest, or in any way demonstrate that their polymeric synthesis produced intact

synthetic super-amphiphilic vesicles in aqueous or any other solution, or that their product could remain intact under dehydration/rehydration conditions or in the presence of an organic solvent. Thus, the cited reference fails to anticipate the claimed invention.

Consequently, it is clear that each of the cited references fails to anticipate Applicants' invention as defined by claims 1-4, 10, 13-15 and 25 under 35 USC § 102(b), since none of the cited prior art teaches the polymeric vesicles of the present invention. Accordingly, Applicants respectfully request that their claims be reconsidered and the rejection be withdrawn.

Response to the rejection under 35 USC §102(a) regarding Hentze

The Examiner has also rejected claims 1-4, 6, 10, 13-18 and 25 under 35 USC § 102(a) as being anticipated by Hentze (*Macromolecules,* 1999). As above, the Examiner reads Hentze as teaching polymeric vesicles having a membrane, wherein the polymers are described in the abstract as diblock polymers. However, Applicants can find no description or mention of "vesicles" in the title, abstract, or results; nor is there any other discussion or demonstration of such. The authors simply describe the formation of bulk lamellar phases and other non-vesicular phases in aqueous solutions that can be regulated by both synthetic tuning of polymer chemistry and physical variables, such as concentration and temperature (see page 5, lines 13-17).

Contrary to the description provided in the specification at page 14, that a vesicular structure must be comprised of a membrane, which separates an internal solution from an external solution, Hentze provides no indication of such. Furthermore, Hentze fails to teach, as compared with the present invention, "preparation and use of vesicles and related encapsulating membranes made in water" (see, *e.g.*, Applicants' Field of Invention), since the structures observed by Hentze are seen strictly in toluene solutions, which is a harsh organic solvent. In addition, vesicles are not simply "lamellar structures," as noted by the examiner in Hentze Figures 4 and 5. Lamellar structures are clearly not "sacs" or "bags" as required for the definition of Applicants' vesicles. As a result, Hentze fails to anticipate the vesicles of the present invention, or Applicants' invention as a whole.

Nevertheless, the Hentze manuscript indicates that it was first received for review by *Macromolecules* on March 18, 1999. By comparison Applicants' manuscript corresponding to the present application was reviewed for publication in *Science* (Discher *et al.*, 1999) in January 1999, several months earlier. A Declaration antedating the cited reference by Applicants'

invention will follow. As such, Hentze is not "prior art." Accordingly, Applicants respectfully request that the claims be reconsidered and that the rejections of claims 1-4, 6, 10, 13-18 and 25 under 35 USC § 102(a) as being anticipated by Hentze - be withdrawn, and the claims found allowable.

Response to the rejection under 35 USC §102(a) regarding Liu

The Examiner has again rejected claims 1-2, 7-8, and 14-18 and 25 under 35 USC § 102(a) as being anticipated by Liu (*Macromolecules,* 1999). The Examiner has maintained his reading of Liu as teaching polymeric vesicles having a membrane, and acryloylphospholipids which are cross-linked (see abstract). However, as explained above with regard to the cited Henzelwood (1998) reference, although Liu teaches cross-linking polymerization of hydrated amphiphiles in monolayers, bilayers and nonlamellar phases, Liu fails to mention or describe the formation of "vesicles" in the manuscript. Instead, the authors simply describe spherical micelles having a diameter comparable to amphiphile dimensions (see, present application at page 3, lines 3-9). However, the disclosed structures are altogether lacking in any sort of membrane that separates an internal solution from an external solution as is defines a vesicle. Hence, Liu fails to anticipate the vesicles of the present invention, or the invention as a whole.

Furthermore, Liu fails to teach, as compared with Applicants' invention, "preparation and use of vesicles and related encapsulating membranes made in water from amphiphilic polymers" (see, *e.g.*, Applicants' Field of Invention). Liu teaches, as does Fendler (1984), the formation of vesicles from lipids, which can be *subsequently* polymerized. As with Fendler, 'polymerized surfactant vesicles' described by Liu are fundamentally different from Applicants' "polymer-surfactant vesicles" in that no more chemistry is required once the latter vesicles – the focus of Applicants' invention - are made.

Nevertheless, the Liu manuscript was received for review by *Macromolecules* on April 8, 1999.. By comparison Applicants' manuscript was reviewed for publication in *Science* (Discher *et al.*, 1999) in January 1999, several months earlier. A Declaration antedating the cited reference by Applicants' invention will follow. As such, Liu is not "prior art." Accordingly, Applicants respectfully request that the claims be reconsidered and that the rejections of claims 1-2, 7-8 and 25 under 35 USC § 102(a) as being anticipated by Liu - be withdrawn, and the claims found allowable.

Accordingly, Applicants respectfully request that all of the § 102 rejections be withdrawn. When examined, each of the cited prior art references quite simply operates in a completely different manner from the present invention. Thus, the prior art fails to define every element of Applicants' invention, meaning that the cited references fail to anticipate the invention. Consequently, Applicants respectfully request that in light of the foregoing, the rejections under 35 USC § 102 (a) and (b) be reconsidered and withdrawn, and the claims held to be fully allowable.

Response to the rejection under 35 USC §103

The Examiner has rejected claims 3-8, 10 and 14-25 under 35 USC § 103 as obvious, over Henzelwood (*Macromolecules,* 1998), Ding (*J. Phys. Chem.*, 1998), Fendler (*Science,* 1998) or Hentze (*Macromolecules,* 1999) for the above-stated reasons. In making this rejection, the Examiner states that each of the cited references suggests potential applications of polymeric vesicles for drug delivery. In addition, the Examiner states that the criticality of the triblock polymer is not apparent from Applicants' invention since it appears that the amphiphilic nature of the polymer is the determining factor. Hence, the Examiner has rejected Applicants' invention.

However, contrary to the Examiner's comments, and as described in detail above, none of the cited references discloses or even suggests the formation of a polymeric vesicle, let alone links how such non-disclosed vesicles could be used for drug delivery. As a result, for the above-identified reasons that the cited references were alone unable to anticipate the present invention, they fail to render Applicants' invention obvious when combined. Even if combined, and further combined with the knowledge of the art at the time of the invention, gaps remain unfilled that could make Applicants' invention obvious to one of ordinary skill in the art with any expectation of success without undue experimentation. These deficiencies cannot been met by combining the references that each failed to stand alone to teach Applicants' invention. Each cited reference fails to teach or suggest Applicants' polymeric vesicles. Thus, even when combined, they cannot teach the formation of a polymeric vesicle, or Applicants' use thereof; and they cannot render Applicants' invention obvious.

The Examiner asserts that "all of the references cited clearly teach the application of these polymers for drug delivery." However, although the references may have a goal of using

the disclosed structure in each for drug delivery, each fails to suggest, even if combined, Applicants' invention, defined as a polymersome vesicle comprising a semi-permeable, thin-walled encapsulating membrane, wherein the membrane is formed in an aqueous solution, and wherein the membrane comprises one or more synthetic super-amphiphilic molecules. In fact, none of the cited references teach polymeric vesicles, which must necessarily contain the following elements: (1) a thin-walled encapsulating membrane, (2) wherein the membrane is formed in an aqueous solution, and (3) wherein the membrane comprises one or more synthetic super-amphiphilic molecules. Consequently although they may propose methods for drug delivery, none render Applicants' claimed invention obvious because none accomplish drug delivery by controlled release from a polymeric vesicle as defined by Applicants in their claimed invention.

Accordingly Applicants again point to the overwhelming differences between the prior art configurations and that of the present invention, none of which are met by the references relied upon by the Examiner. The present invention quite simply operates in a completely different manner from the prior art, and produces vesicles that have a multitude of uses, none of which have been previously possible. Thus, the prior art fails to render Applicants' invention obvious, and Applicants respectfully request that in light of the foregoing, the rejection under 35 USC § 103 be reconsidered and withdrawn.

In sum, Applicants assert that all pending claims are in condition for allowance, and respectfully request that allowance be granted at the earliest date possible. Should the Examiner have any questions or comments regarding Applicants' amendments or response, he is asked to contact Applicants' undersigned representative at (215) 575-7034.

Respectfully submitted

Date: May 20, 2002

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Version with markings to show changes made

In the claims:

Claims 21-22 and 24 have been cancelled.

Claims 15 and 16 have been amended as follows:

15. (Twice Amended) A method of using the polymersome vesicle of claim 3, wherein the method comprises:

preparing the polymersome vesicle; and

[~~transporting~~] importing into the polymersome at least one encapsulatable material [~~to or~~] from the environment immediately surrounding the polymersome, thereby encapsulating the at least one material within the polymersome and removing it from the surrounding environment.

16. (Twice Amended) The method of claim 15, wherein the environment is in a patient, and wherein the method further comprises [~~transporting~~] importing the encapsulatable material to [~~or from~~] the patient, thereby permitting delivery to the patient.

New claims 26-28 were added.